

## Don't Let the "Bad Bugs" Bite - Hamamelitannin Analogues as Adjuvants for Vancomycin in the Treatment of MRSA Biofilm Infections.

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For the last decades, antibacterial research and development has focused on drugs that kill bacteria or inhibit their growth by interfering with essential cellular processes. Conventional antibiotics inherently impose selective pressure on bacteria and microbial drug resistance constitutes a complex global public health challenge. In this project we aim to design small molecules that potentiate the effect of existing antibiotics. More specifically, we want to synthesize compounds that target virulence factors and biofilm formation in *Staphylococcus aureus* and hence sensitize 'golden staph' towards antibiotic treatment. With careful consideration, we believe that these "antivirulence" drugs have a lower propensity to select for resistance.

Recently, Kiran *et al.* discovered hamamelitannin (HAM, Figure): a small molecule that prevents biofilm formation and increases the susceptibility of *S. aureus* towards vancomycin treatment. HAM is a natural substance isolated from the witch hazel (*Hamamelis virginiana*) and represents an interesting lead for further optimization. However, the stability and activity of this natural molecule are not optimal. Hit-to-lead optimisation of HAM led to the identification of compound **2**, a metabolically stable derivative with potent *in vitro* activity (0.389  $\mu$ M), exceptional activity in a *C. elegans* infection model and a murine mastitis model, while lacking cytotoxicity against MRC-5 lung fibroblast cells.

